CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761202Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 10, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761202
Product Name and Strength:	Byooviz (ranibizumab-nuna) injection, 0.5 mg
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd
OSE RCM #:	2020-1963-1
DMEPA 1 Safety Evaluator:	Nasim Roosta, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), container label, and carton labeling received on August 13, 2021 for Byooviz. The Division of Ophthalmology (DO) requested that we review the revised prescribing information, container label and carton labeling for Byooviz (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a], as well as recommendations communicated by DO.[b]

2 CONCLUSION

The proposed container label and carton labeling may be improved to promote safe use of this product from a medication error perspective.

The Applicant clarified that the expiration date format they intend to use on the container labels and carton labeling will be "YYYYMMMDD (e.g., 2021JAN01)," which we find acceptable.

As part of our evaluation of the revised container labels and carton labeling, we note that some but not all of our previous recommendations[a] pertaining to the container label and carton labeling were communicated to the Applicant. As a result, the Applicant did not implement some of our recommendations. Specifically, the Applicant was not informed to revise the

[a] Roosta, N. Label and Labeling Review for Byooviz (BLA 761202). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 JUL 1. RCM No.: 2020-1963.
[b] Information Request: BLA 761202 carton container FDA comments. Silver Spring (MD): FDA, CDER, DO (US). 2021 AUG 04. Available at: \\CDSESUB1\evsprod\bla761202\0037\m1\us\ir-req-comments-advice-2021aug04.pdf

presentation of their proprietary name such that all letters appear in one color font. While we maintain that the current presentation (i.e., use of different color font to highlight a portion of the name) should be reserved for instances when a safety concern has been identified that necessitates additional mitigation strategies, we find that the current presentation is not likely to result in the proprietary name appearing similarly to another product name on the market and lead to name confusion. Thus, we have no additional comments pertaining to this issue at this time.

We note that a recommendation to change the strength expression from "0.5 mg/0.05 mL" to "0.5 mg" was included in the container label and carton labeling comments communication sent to the Applicant dated August 4, 2021.[c] We confirmed with our Office of Pharmaceutical Quality colleagues that each vial of Byooviz is filled with 0.23 mL to deliver a 0.05 mL dose volume. Therefore, we are concerned that the overfill amount and lack of a net volume or dose volume statement could result in dosing errors. We discussed the change with DO, who noted that because Byooviz is a biosimilar to Lucentis (BLA 125156) the strength presentation was revised to align with Lucentis. Additionally, DO noted that Lucentis has a fill volume of 0.3 mL, which is designed to deliver a 0.05 mL dose. Therefore, the overfill amount for Byooviz does not present an increased risk to dosing errors compared to what is already present on the market for ranibizumab. Given that we are not aware of postmarket reports that describe confusion with the strength presentation on Lucentis single-dose vials, we do not object to the change in strength presentation on Byooviz to align with Lucentis but recommend for future consideration that the dose volume be included on these products to provide clarity to end users, for example, "contains overfill to allow for administration of 0.X mL dose" or a similar statement. Additionally, we provide a recommendation to revise the *Dosage Forms and Strengths* section of the prescribing information to align the strength presentation across the labels and labeling (see Section 3).

We note that the Applicant revised the carton labeling to include the statement, "discard unused portion," immediately following the package-type term "single dose vial," but did not include the same revision on the container label. Therefore, we provide recommendation for the Applicant to include "Discard unused portion" immediately following the package type term on the container label (see Section 3).

3 RECOMMENDATIONS FOR SAMSUNG BIOEPIS CO., LTD

We recommend the following be implemented prior to approval of this BLA:

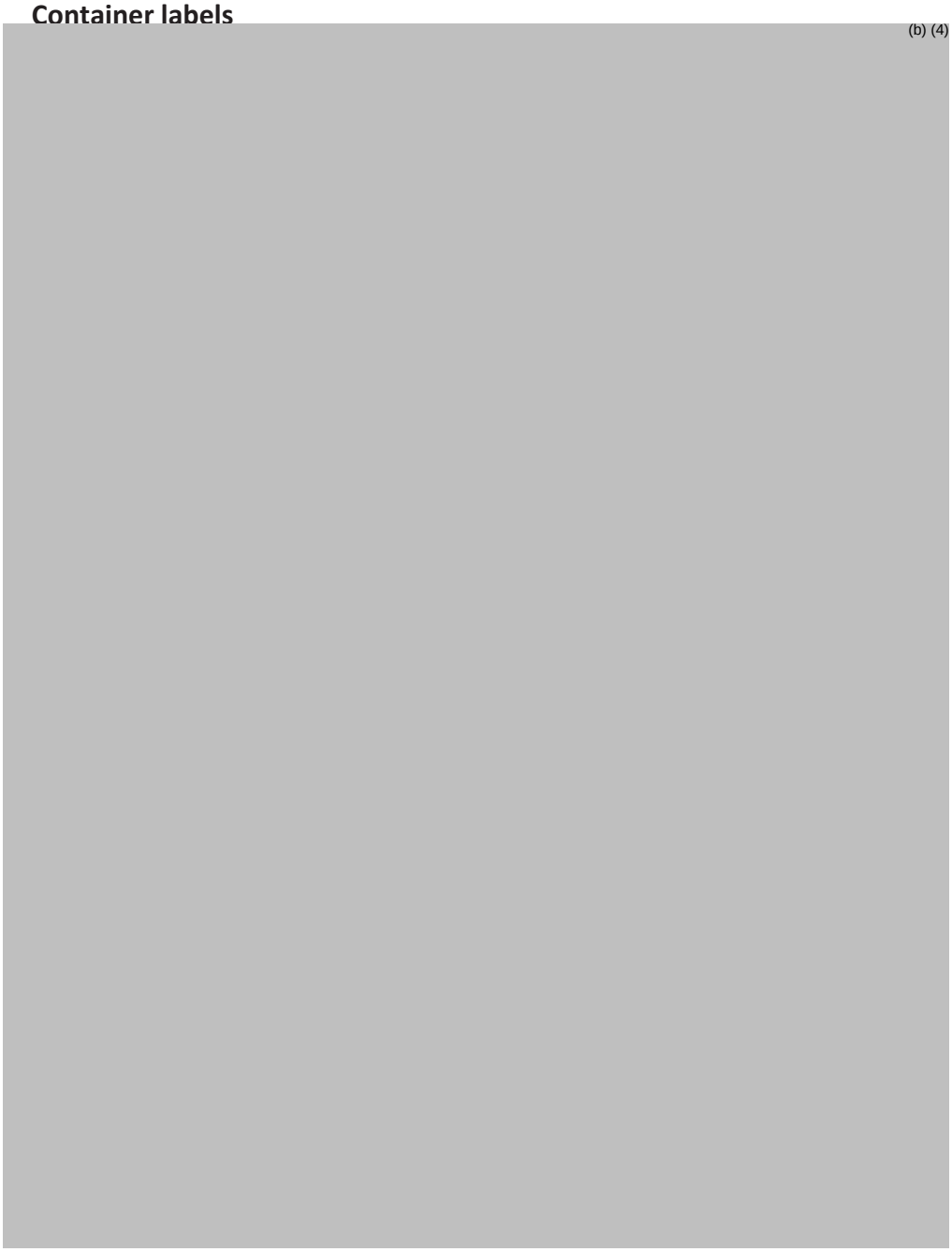
A. We recommend including the statement "Discard unused portion" following the single-dose vial statement on the back panel of the vial.
B. In the *Dosage Forms and Strengths* section of the Highlights of Prescribing Information and Full Prescribing Information, include the intended dosage in mg units immediately after the dose volume so that the first line reads "Single-dose glass vial designed to provide 0.05 mL (0.5 mg) for intravitreal injection…"

[c] Information Request: BLA 761202 carton container FDA comments. Silver Spring (MD): FDA, CDER, DO (US). 2021 AUG 04. Available at: \\CDSESUB1\evsprod\bla761202\0037\m1\us\ir-req-comments-advice-2021aug04.pdf

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 13, 2021

Container labels

(b) (4)



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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 8/2/21

To: Lois Almoza, Regulatory Project Manager, (OSM/DO)

Lucious Lim, M.D.
Division of Ophthalmology Products (OSM/DO)

From: James Dvorsky, Team Lead
Office of Prescription Drug Promotion (OPDP)

CC: Carrie Newcomer, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for Byooviz (ranibizumab-nuna)

BLA: 761202

In response to the OSM consult request dated November 12, 2020, OPDP has reviewed the proposed product labeling (PI) and carton/container labeling for the original BLA submission for Byooviz (ranibizumab-nuna), a biosimilar to Lucentis (ranibizumab injection).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received electronically from OSM on 7/28/21 and there are no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received electronically from OSM on 8/2/21, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact James Dvorsky at (301) 796-2655 or james.dvorsky@fda.hhs.gov

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JAMES S DVORSKY
08/02/2021 01:25:55 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 1, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761202
Product Name and Strength:	Byooviz (ranibizumab-xxxx[a]) injection, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Samsung Bioepis Co., Ltd
FDA Received Date:	September 17, 2020
OSE RCM #:	2020-1963
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Valerie Vaughan, PharmD

[a] The nonproprietary name suffix for this BLA has not yet been determined; therefore, the placeholder, ranibizumab-xxxx, is used throughout this review to refer to the nonproprietary name and suffix for this product.

1 REASON FOR REVIEW

As part of the approval process for Byooviz (ranibizumab-xxxx) injection, the Division of Ophthalmology (DO) requested that we review the proposed Byooviz prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information, container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information, Container Label and Carton Labeling			
1.	The non-proprietary name suffix is denoted by the placeholder “-xxxx”.		Replace “-xxxx” with the conditionally acceptable non-proprietary name suffix, when it is determined.

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	We note the use of the package type term "single-use" to describe the product in the Prescribing Information (PI), container label and carton labeling.	"Single-use" is not considered an appropriate package type term.[b]	We recommend revising the package type term to "single dose" throughout the labels and labeling.
3.	As currently presented, the units of temperature measurement (Centigrade and Fahrenheit) are not included following the first numeric degree measurement in the temperature ranges.	The lower temperatures in the ranges may be overlooked.	We recommend revising the storage statement to include the Centigrade symbol (°C) and Fahrenheit symbol (°F) following each numeric degree measurement of temperature ranges. For example, "2°C - 8°C (36°F - 46°F)".
Prescribing Information- General			
1.	The proprietary name placeholder is displayed as "SB11"; however, the proprietary name "Byooviz" was found conditionally acceptable on 12/14/2020.[c]		Update the PI to replace "SB11" with the conditionally acceptable proprietary name, "Byooviz".
Prescribing Information- Section 16: How Supplied/Storage and Handling			
1.	Section 16 describes storage for a prefilled syringe; however, the proposed product will be supplied as a vial only.	Failure to omit an inapplicable dosage form could lead to confusion.	Remove reference to a prefilled syringe in Section 16 so that the sentence reads "Protect vials from light and store in the original carton until time of use."

[b] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from: https://www fda.gov/media/117883/download

[c] Getahun, S. Proprietary Name Review for Byooviz (BLA 761202/S-0001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 14. Panorama No. 2020-42853608.

Table 3. Identified Issues and Recommendations for Samsung Bioepis Co., Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Carton Labeling			
1.	The format for the expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The letter string “o-o” of the proprietary name, Byooviz, is in a different color font (light green) than the remaining letters of the name (“B-y” and “v-i-z”).	Typically, methods used to highlight a portion of the name (e.g., tallman lettering or different font color) are reserved for use when a safety concern has been identified that necessitates additional mitigation strategies.	We recommend that you revise the proprietary name, Byooviz, such that all letters appear in one color of font.
3.	As currently presented, the “Usual Dosage”	Per 21 CFR 201.55, “…labels for prescription drugs	To ensure consistency with the Prescribing Information, revise

Table 3. Identified Issues and Recommendations for Samsung Bioepis Co., Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	statement is not consistent with the recommended dosage statement in the prescribing information.	should bear a statement of the recommended or usual dosage." Additionally, the "Usual Dosage" statement should be aligned with the Prescribing Information.	the statement, "Usual dose: See Prescribing Information" on the container label and carton labeling to read "Recommended Dosage: See Prescribing Information."
4.	We note the use of the package type term "single-use" on the container label and carton labeling. Additionally, the container label and carton labeling lacks an appropriate discard statement.	"Single-use" is not considered an appropriate package type term.[d] Additionally, including an appropriate discard statement will facilitate proper handling of the product.	We recommend revising the package type term to "single dose" and including the discard statement "discard unused portion immediately following or in close proximity to the package type term. For example: "Single dose vial – Discard unused portion"
Carton Labeling			
1.	On the principal display panel (PDP) immediately to the right of the strength statement, abbreviations for the proposed indications are displayed, which compete in prominence with critical information such as the strength and non-proprietary name.	As currently presented, the abbreviations for the proposed indications distract from the presentation of required critical information on the PDP of the carton labeling. Additionally, these abbreviations are redundant and create visual labeling clutter as the indications are outlined below the strength statement.	Delete the indication abbreviations immediately to the right of the strength statement on the PDP of the carton labeling. For example: change **"0.5 mg/0.05 mL l wAMD l RVO l mCNV"** to **"0.5 mg/0.05 mL".** For more information, see Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.[e]

[d] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from: https://www fda.gov/media/117883/download

[e] When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/regulatory-information/search-fda-guidance-documents.

Table 3. Identified Issues and Recommendations for Samsung Bioepis Co., Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	The established name is not at least half the size of the proprietary name.	In accordance with 21 CFR 201.10(g)(2), the established name should be printed in letters that are at least half as large as the letters comprising the proprietary name and be of commensurate prominence to the proprietary name.	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
3.	The product's indications are displayed on the PDP of the carton labeling more prominently than other important information, for example, the non-proprietary name.	Critical product information such as the proprietary name, non-proprietary name, product strength, route of administration, and warnings or cautionary statements, if any, should appear as the most prominent information on the PDP.	We recommend decreasing the prominence of the indications, for example, by decreasing the font size. Additionally, we recommend increasing the prominence of the non-proprietary name, for example, by increasing the font size. Ensure the font size of the non-proprietary name is at least ½ the size of the proprietary name.

4 CONCLUSION

Our evaluation of the proposed Byooviz prescribing information, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Samsung Bioepis Co., Ltd so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Byooviz that Samsung Bioepis Co., Ltd submitted on September 17, 2020.

Table 4. Relevant Product Information for Byooviz	
Initial Approval Date	N/A
Active Ingredient	ranibizumab
Indication	Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), and Myopic Choroidal Neovascularization (mCNV)
Route of Administration	Intravitreal
Dosage Form	injection
Strength	10 mg/mL
Dose and Frequency	Neovascular (Wet) Age-Related Macular Degeneration - 0.5 mg (0.05 mL) once a month (approximately 28 days). - Although not as effective, may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. - Although not as effective may be treated every 3 months after 4 monthly doses. Patient should be assessed regularly. Macular Edema Following Retinal Vein Occlusion - 0.5 mg (0.05 mL) once a month (approximately 28 days) Myopic Choroidal Neovascularization - 0.5 mg (0.05 mL) once a month (approximately 28 days) for up to three months. May be retreated if needed.
How Supplied	Each 0.5 mg carton contains a single-use, 2-mL glass vial designed to deliver 0.05 mL of 10 mg/mL ranibizumab solution
Storage	Refrigerated at 2°C – 8°C (36°F – 46°F). DO NOT FREEZE. Protect from light and store in the original carton until time of use.
Container Closure	The container closure system (b) (4) single use containers.

APPENDIX F. LABELS AND LABELING

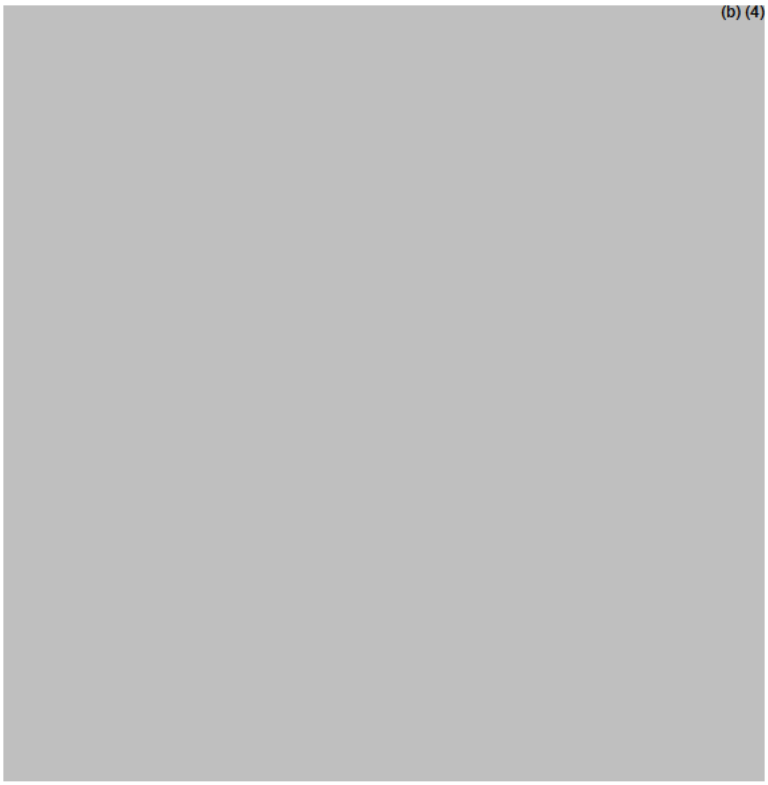
F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Byooviz labels and labeling submitted by Samsung Bioepis Co., Ltd.

- Container label received on September 17, 2020
- Carton labeling received on September 17, 2020
- Prescribing Information (Image not shown): \\CDSESUB1\evsprod\bla761202\0001\m1\us\draft-labeling-text-highlights-pi-clean.pdf

F.2 Label and Labeling Images

Container label:



[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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07/01/2021 01:55:15 PM

Clinical Inspection Summary

Date	July 01, 2021
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Lucious Lim, M.D., M.P.H., Medical Officer William Boyd, M.D., Clinical Team Leader Lois Almoza, M.S., Regulatory Project Manager Division of Ophthalmology
BLA #	761202
Applicant	Samsung Bioepsis Co., Ltd.
Drug	ranibizumab (proposed biosimilar to Lucentis®)
NME (Yes/No)	Yes
Review Priority	Standard
Proposed Indication(s)	Treatment of neovascular age-related macular degeneration, macular edema secondary to retinal vein occlusion and myopic choroidal neovascularization
Consultation Request Date	November 05, 2020
Summary Goal Date	July 16, 2021
Action Goal Date	September 01, 2021
PDUFA Date	September 17, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study SB11-G31-AMD was submitted to the Agency in support of this Biologic License Application (BLA) 761202 for ranibizumab (proposed biosimilar to Lucentis®) on 09/18/2020. Lucentis® was approved on 06/30/2006 for the treatment of neovascular age-related macular degeneration (AMD), macular edema secondary to retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV). Three clinical investigators (CIs): Drs. Sunil Patel (Site 2812), James Luu (Site 2816) and Atul Jain (Site 2821) were selected for clinical inspections.

The inspections verified the sponsor Samsung Bioepsis Co., Ltd. (Samsung) submitted clinical data with source records at the CI sites. Based on the results of these inspections, Study SB11-G31-AMD appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Samsung submitted BLA 761202 for ranibizumab (biosimilar to Lucentis®) on 09/18/2020. The proposed indication is for the treatment of neovascular AMD, macular edema secondary to RVO and mCNV. Data from a Phase 3 study SB11-G31-AMD were submitted to support the approval of the BLA.

Study SB11-G31-AMD

Study SB11-G31-AMD was a Phase 3, randomized, double-masked, parallel group, multicenter study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between ranibizumab (SB11) and Lucentis® in subjects with neovascular AMD. The primary study objective was to demonstrate the equivalence of efficacy of ranibizumab to that of Lucentis® in subjects with neovascular AMD. The primary efficacy endpoint was the change from baseline in best corrected visual acuity (BCVA) at Week 8.

Eligible subjects were randomly assigned in a 1:1 ratio to receive either 0.5 mg ranibizumab (SB11) or 0.5 mg Lucentis® via intravitreal (ITV) route every 4 weeks up to Week 48. Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse visual acuity (VA) was selected as the study eye. If both eyes had equal VA, the eye with a better visual prognosis (e.g., clearer lens and ocular media, and less amount of sub-foveal scar or geographic atrophy) was selected. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology, and subject preference were considered in making the selection.

The study screened a total of 1095 subjects and enrolled 705 subjects at 75 study sites in 9 countries (Czech Republic, Germany, Hungary, India, Poland, Republic of Korea, UK, and US). The first subject was enrolled on 03/14/2018 and the last subject completed the study on 12/09/2019.

Rationale for Site Selection

Three CIs: Drs. Sunil Patel (Site 2812), James Luu (Site 2816) and Atul Jain (Site 2821) were requested for clinical inspection in support of the application. These sites were selected based on enrolling a high number of patients to the study treatment arms that may have an impact in the review division's clinical decision-making process.

III. RESULTS

1. Dr. Sunil Patel, Site 2812

5441 Health Center Drive
Abilene, Texas 79606

This CI was inspected on 01/12-15/2021 as a data audit for Study SB11-G31-AMD. This was the second inspection for Dr. Patel. Previous inspection on 09/17-21/2012 was voluntary action indicated (VAI) with FDA 483 (Inspectional Observations) due to "failed to report all protocol deviations" and "failed to maintain temperature log for the investigational product (IP) refrigerator".

The study site screened a total of 30 subjects, enrolled 17 subjects, with all 17 subjects completed the study. The first subject was enrolled on 04/20/2018 and the last subject's last follow-up visit was on 10/30/2018. All source records were reviewed for all of the 17 enrolled subjects and the 13 screen failure subjects.

Source records reviewed during the inspection included the study protocol and amendments, informed consent forms (ICFs), documentation of eligibility criteria and enrollment logs, medical

records [including monitoring logs, ophthalmological exam results, laboratory tests, adverse events (AEs)/serious AEs (SAEs)], IP accountability records, visit data, case report forms (CRFs), protocol deviations and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, staff training logs, financial disclosures and delegation of authority].

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs. Observations from the previous 2012 inspection were corrected.

At the end of the inspection, a Form 483 was not issued. There were no discussion items. The clinical site appeared to be in compliance with Good Clinical Practice (GCP).

2. Dr. James Luu, Site 2816
2770 North Union Blvd., Suite 140
Colorado Springs, CO 80909

This CI was inspected on 12/14-18/2020 as a data audit for Study SB11-G31-AMD. This was the first FDA inspection for Dr. Luu. The study site screened 31 subjects, enrolled 22 subjects, with 20 subjects completed the study. The first subject was enrolled on 03/29/2018 and the last subject's last follow-up visit was on 10/30/2019. All source records for all of the 22 enrolled subjects were reviewed.

Source records reviewed during the inspection included study protocol and amendments, ICFs, documentation of eligibility criteria and enrollment logs, medical records (including monitoring logs, ophthalmological exam results, blood tests, AEs/SAEs, concomitant medication use), IP accountability records, electronic CRFs (eCRFs) with electronic data capture (EDC), protocol deviations, and related regulatory documents (e.g., IRB approvals and communications, staff training logs, financial disclosures and delegation of authority).

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy endpoint was verified. There was no evidence of underreporting of AEs or SAEs.

At the end of the inspection, a Form 483 was issued for an observation that an investigation was not conducted in accordance with the investigational plan. Specifically, the primary endpoint measurement of Best Corrected Visual Acuity (BCVA) assessment was conducted in a non-certified Visual Acuity Examination Room for 8 subjects ([redacted] (b) (6) one visit each when the light bulb of the examination room was replaced on 07/25/2019, but was not recertified until 08/12/2019.

Reviewer's Comments: Although BCVA assessment for 8 subjects was not performed at one of the visits according to the protocol, which is a regulatory violation, the finding has been reported as

protocol deviation in the CSR. The violation is unlikely to impact data reliability assessment or to impact the rights, safety, and welfare of subjects in the study. The CI responded to the Form 483 on 01/08/2021 that the incidences were reported to the sponsor as minor protocol deviations and were included in the submission. The CI has certified a second visual acuity room for the study after the incidences.

One item discussed at the end of the inspection: expired (1-2 months past) urinalysis test strips were used for 9 subjects: (b) (6) during Visit 16.

Reviewer's Comments: The CI responded that these were reported to the sponsor as protocol deviations. The CI acknowledged the overlook and implemented changes for improvement. All of the above identified issues were included in the submission as protocol deviations.

In general, this clinical site appeared to be in compliance with GCP except the items noted above. These findings appear unlikely to have significant impacts on the overall efficacy and safety results.

3. Dr. Atul Jain, Site 2821
12630 Monte Vista Road, Suite 104
Poway, CA 92064

This CI was inspected on 12/07-11/2020 as a data audit for Study SB11-G31-AMD. This was the first inspection for Dr. Jain. The study site screened a total of 16 subjects, enrolled 11 subjects, with 10 subjects completed the study. The first subject was enrolled on 04/09/2018 and the last subject's last follow-up visit was on 12/09/2019. All source records for the 16 screened subjects (11 enrolled and 5 screen failure subjects) were reviewed.

Source records reviewed during the inspection included study protocol and amendments, ICFs, documentation of eligibility criteria and enrollment logs, medical records (including monitoring logs, visit reports, laboratory tests, AEs, concomitant medication use), IP accountability records, CRFs with eCRFs entries and EDC, protocol deviations, and related regulatory documents (e.g., IRB approvals and communications, staff training logs, financial disclosures and delegation of authority).

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy endpoint was verified. There was no evidence of underreporting of AEs or SAEs.

At the end of the inspection, a Form 483 was not issued. Discussed items were:

- Subject (b) (6) SAE of hospitalization for new onset of atrial fibrillation occurred on (b) (6) was not signed off by the CI until 03/07/2019.
- Subject (b) (6) was consented with an "invalid" ICF that the sponsor provided on 10/08/2018 and was reconsented on 10/11/2018.

- Subject [redacted] (b) (6) prior use of Xanax was not listed in the eCRF/EDC or the submitted data listing. Subject [redacted] (b) (6) concomitant medications log was incomplete.
- The CI could not locate the central lab's CLIA certificate for 2018.

Reviewer's Comments: The discussed items are unlikely to impact data reliability or to compromise the rights, safety, and welfare of subjects in the study. The CI acknowledged the overlook and implemented changes for improvement.

In general, this clinical site appeared to be in compliance with GCP except the items noted above. These findings appear unlikely to have significant impacts on the overall efficacy and safety results.

{See appended electronic signature page}

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/s/

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